REMARKS

Claims 16, 17, 24, 25, 27, 44-46, 48-50, 70-89 and 117-130 are pending in the application. Claims 44, 45, 70, 76, 77, 81, 85, 86, 89, 119, 121, 122 and 130 have been amended. The amendments to the claims are chiefly ministerial in nature. The amendments to claims 44 and 121 are supported throughout the specification and original claims. See for example, paragraphs 104-110. In the May 30, 2008. Office Action claims 45, 70-89, and 119-130 were rejected under 35 USC § 112, second paragraph, as indefinite. All pending claims were rejected under 35 USC § 103(a) as obvious over Spence in view of Chou and Singhvi. The specific grounds of rejection, and applicants' response thereto, are set forth in detail below..

Rejections under 35 USC § 112, second paragraph

The Examiner suggested appropriate claim language to overcome the various rejections. Applicants thank Examiner Ware for these helpful suggestions and have amended the claims in the manner suggested, thereby obviating the rejection.

Rejections under 35 USC § 103(a)

All pending claims are rejected under 35 USC § 103(a) as obvious over Spence in view of Chou and Singhvi. Specifically, the Examiner asserts that Spence teaches a method of producing a cell population enriched in a first cell, that Singhvi teaches a device containing obstacles separated by gaps where cells bind to the obstacles, and Chou teaches that the obstacles may be pillars. The Examiner goes on to assert that one of ordinary skill in the art would have been motivated to combine the techniques described in the cited references to "enhance cell population concentration and to achieve improved results." Applicants respectfully traverse.

The instant claims recite that the claimed methods use a microfluidic device having a series of obstacles in a channel separated by gaps, whereby flow of a blood sample through the device causes cells to be directed in one direction or another based on size. Spence describes methods that use an altogether different device:

> The invention provides a microfabricated device for sorting cells based on a desired characteristic, for example, reporter-labeled cells can be sorted by the presence or level of reporter on the cells. The device includes a chip having a substrate into which is microfabricated at least one analysis unit. Each analysis unit includes a main channel, having a sample inlet channel, typically at one end, and a detection region along its length. Adjacent and downstream from the

> detection region, the main channel has a discrimination region or branch point leading to at least two branch channels. The analysis unit may further include additional inlet channels, detection points, branch points, and branch channels as desired. A stream containing the cells, e.g., in a solution or mixture, is passed through the detection region, such that on average only one cell occupies the detection region at any given time. The cells can be sorted based on their ability to emit a detectable signal such as an optical signal, with or without stimulation, such as exposure to light in order to promote fluorescence. According to the invention, the presence or level of reporter from each cell is measured within the detection region, and each cell is directed to a selected branch channel based on the level of reporter detected or measured.

Spence at paragraph 9. Spence uses the term "channel" in a conventional manner to refer to the conduit through which a sample may flow. Although Spence explicitly states that the device contains one or more channels, nowhere does Spence teach or suggest that any channel contains obstacles *within the channel.* Rather, Spence shows *at most* multiple channels – see Figure 5, for example, but no reasonable interpretation of Spence would conclude that the large blocks of material that define the channels somehow represents "obstacles" within a single channel.

Nor does Spence teach a method where flow of the sample past a series of obstacles device causes cells to be directed in one direction or another based on size. Rather, Spence describes methods that rely on detection of a property of each cell as it passes through a detection window in the device. As Spence describes, "[c]ells are diverted into one or another outlet channel based on a predetermined characteristic that is evaluated as each cell passes through the detection region." (page 2, [0012]). Thus Spence requires a separate selection step and fails to teach or suggest a method where flow of a sample past obstacles in a channel *causes* separation.

Indeed, although Spence purports to describe, *inter alia,* separation based on size, it is not clear how the device described by Spence could achieve such a separation. Although Spence describes in detail various detection protocols for selecting cells in a sample (for example, based on the presence or absence of a fluorescent label), there is no description of how any size-based selection could be carried out. Accordingly, applicants respectfully submit that Spence fails to enable a method for size-based separation.

Singhvi merely describes a substrate that permits selective binding of cells to some areas of the substrate. This device is merely static and Singhvi neither teaches nor suggests methods

using a microfluidic device through which a sample flows past a series of obstacles in a channel. Applicants respectfully submit that there would have been no motivation to combine Singhvi's static device with Spence's flow-based device. Indeed, there is no indication in Singhvi that the static device may be used in flow-based methods. In the absence of a proper motivation to combine the references, applicants respectfully submit that rejection is improper and should be withdrawn.

Chou merely shows support pillars in a channel, and fails to teach or suggest that sample flow past these pillars has *any* effect at all on the sample, let alone permit size-based or affinity-based separation of cells in the sample.

In sum, none of the cited references, nor their combination, teaches or suggests methods that use a microfluidic device having a series of obstacles in a channel separated by gaps, whereby flow of a blood sample through the device causes cells to be directed in one direction or another based on size, nor do the references teach or suggest that such a device should be combined with a flow-based separation that relies on selective binding. Accordingly, no *prima facie* case of obviousness exists and applicants respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing amendments, Applicants respectfully submit that the application is in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-3840. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. §1.136(a)(3).**

Respectfully submitted,

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